DETAILED ACTION

Formal Matters

1. The Examiner of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Kimberly Ballard, Art Unit 1649.

Response to Amendment

2. Claims 210, 211, and 214 have been amended as requested in the amendment filed on 18 December 2008. Following the amendment, claims 177 and 210-214 are pending in the instant application.

Claims **177** and **210-214** are under examination in the instant office action.

Information Disclosure Statement

3. Signed and initialed copies of the IDS papers filed 19 December 2008 are enclosed in this action.

Reissue Applications

4. Applicant is reminded of the continuing obligation under 37 CFR 1.178(b), to timely apprise the Office of any prior or concurrent proceeding in which Patent No. 5,688,651 is or was involved. These proceedings would include interferences, reissues, reexaminations, and litigation.

Applicant is further reminded of the continuing obligation under 37 CFR 1.56, to timely apprise the Office of any information which is material to patentability of the claims under consideration in this reissue application.

These obligations rest with each individual associated with the filing and prosecution of this application for reissue. See also MPEP §§ 1404, 1442.01 and 1442.04.

Withdrawn Objections and Claim Rejections

5. The objection to the application under 37 CFR 1.172(a) as lacking the written consent of all assignees, set forth at page 3 of the previous office action (06/19/2008), is withdrawn in view of Applicant's notification that such consent was filed on May 25, 2001.

6. The rejection of claims 177 and 210-214, for being based upon a defective reissue oath under 35 U.S.C. 251, set forth at page 3 of the previous office action (06/19/2008), is withdrawn in view of Applicant's submission of a supplemental declaration under 37 CFR 1.175 (filed December 18, 2008).

7. The objection to the specification under 37 CFR 1.177(a), regarding the notice of multiple reissue applications and Applicant's duty to provide such notice, is withdrawn in view of Applicant's amendment to the specification filed December 18, 2008. As noted by Applicant, more than one reissue application has been filed with respect to the

present patent, the first being the instant application (no. 09/441,140, filed November 16, 1999), and the second, which is a divisional of the first, being application no. 11/358,951, filed February 22, 2006.

8. The rejection of claims 177, 210, 211 and 214 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement (new matter rejection), is withdrawn in view of Applicant's arguments.

9. The rejection of claims 210 and 211 under 35 U.S.C. 102(a) as being anticipated by Bickel et al. (1994) is withdrawn in view of Applicant's amendments to the claims.

10. The rejection of claims 210 and 211 under 35 U.S.C. 102(b) as being anticipated by Stern et al. (1989) is withdrawn in view of Applicant's amendments to the claims.

11. The rejection of claims 210 and 211 under 35 U.S.C. 102(a) as being anticipated by Walker et al. (1994) is withdrawn in view of Applicant's amendments to the claims.

12. The rejection of claims 210 and 211 under 35 U.S.C. 102(e) as being anticipated by Suzuki et al. (US Patent No. 5,750,349) is withdrawn in view of Applicant's amendments to the claims.

13. The Gershoni declaration under 37 CFR 1.132 filed December 18, 2008 is sufficient to overcome the rejection of claims 210-213 based upon anticipation under 35 U.S.C. 102(b). Specifically, the declaration provides expert testimony by Dr. J.M. Gershoni concluding that it would be highly unlikely to expect that a synthetic Aβ peptide consisting of residues 1-28 would be able to elicit antibodies similar to the human monoclonal antibodies described by Gaskin et al. (1993).

14. The declaration filed on 19 March 2007 under 37 CFR 1.131 along with the supplemental declarations of Kohn, Hirsch, and Browdy (also filed 19 March 2007) are sufficient to antedate the Anderson reference (US Patent No. 5,589,154) in view of Applicant's arguments filed 18 December 2008 and submission of case law pertaining to the instant fact pattern. In particular, *Ex Parte Hachiken*, 223 USPQ 879, 880 (Bd. Pat. App. 1984) states that "the date of a draft application originating in a foreign country is introduced into this country by way of counsel may be taken as the date of conception of the invention in this country." In view of this newly submitted case law, the evidence submitted in the declarations filed 19 March 2007 is sufficient to establish a date of conception of the instant invention prior to that of the Anderson filing date of November 22, 1994.

Accordingly, the rejection of claims 177 and 210-213 under 35 U.S.C. 102(e) as being anticipated by Anderson et al., US Patent No. 5,589,154, is withdrawn in view of the declarations under 37 CFR 1.131 noted above.

15. The rejection of claims 177, 212 and 213 under 35 U.S.C. 103(a) as being obvious over either Bickel et al. (1994) or Stern et al. (1989), in view of Becker et al. (EP 0613007 A2) and Anderson et al. (US 5,589,154), is withdrawn in view of Applicant's arguments and the declarations under 37 CFR 1.131 noted above.

16. The rejection of claim 177 under 35 U.S.C. 103(a) as being obvious over Gaskin et al. (1993) in view of Becker et al. (EP 0613007 A2) and Anderson et al. (US 5,589,154), is withdrawn in view of Applicant's arguments and the declarations under 37 CFR 1.131 noted above.

17. The rejection of claims 177, 212 and 213 under 35 U.S.C. 103(a) as being obvious over Walker et al. (1994) in view of Becker et al. (EP 0613007 A2) and Anderson et al. (US 5,589,154), is withdrawn in view of Applicant's arguments and the declarations under 37 CFR 1.131 noted above.

18. The rejection of claims 177, 212 and 213 under 35 U.S.C. 103(a) as being obvious over Suzuki et al. (US Patent No. 5,750,349) in view of Becker et al. (EP 0613007 A2) and Anderson et al. (US 5,589,154), is withdrawn in view of Applicant's arguments and the declarations under 37 CFR 1.131 noted above.

New Claim Rejections and/or Objections

Claim Rejections - 35 USC § 112, first paragraph

19. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

20. Claims 177 and 210-214 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 177 and 210-211 encompass to a therapeutic composition comprising a pharmaceutically acceptable carrier and a genetically-engineered antibody that inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid, or a fragment of said antibody, wherein said genetically-engineered antibody is obtained by genetically engineering the DNA encoding a monoclonal antibody that (i) inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid and (ii) is obtainable using a peptide consisting of residues 1-28 of beta-amyloid as an immunogen or recognizes an epitope within residues 1-28 of beta-amyloid, wherein the genetically-engineered monoclonal antibody is a single-chain antibody. Claim 177 is limited to single chain antibodies. Claim 211 is limited to human beta-amyloid. Claims 212 and 213 are drawn to similar therapeutic compositions comprising a human monoclonal antibody. Claim 214 is drawn to a method of making a therapeutic

composition comprising a pharmaceutically acceptable carrier and a genetically-engineered antibody or fragment thereof, comprising selecting a monoclonal antibody that (i) inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid, and (ii) is obtainable using a peptide consisting of residues 1-28 of beta-amyloid as an immunogen or recognizes an epitope within residues 1-28 of beta-amyloid; genetically engineering the DNA encoding said selected monoclonal antibody so as to produce a genetically-engineered antibody or fragment thereof having the aforementioned anti-aggregation properties; and formulating said genetically-engineered monoclonal antibody or fragment with a pharmaceutical carrier into a therapeutic composition. The phrase "genetically-engineered antibodies" is given its broadest reasonable interpretation, specifically, it is not limited to single-chain antibodies, but instead broadly encompasses humanized, chimeric, veneered, resurfaced, CDR-grafted and other such engineered antibodies. Because the claims recite the broadly encompassing genus of genetically-engineered antibodies and human monoclonal antibodies, they are considered genus claims. Even with respect to claims 177 (limited to single chain antibodies)and 212-213 (drawn to human monoclonal antibodies), the claims encompass a genus of antibody molecules differing in structure and epitope specificity.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of

making the claimed product, or any combination thereof. In this case, the only factors present in the claims are a recitation of the desired functional inhibitory and generic binding characteristics and/or the peptide fragment used as an immunogen to obtain the monoclonal antibody from which the claimed genetically-engineered antibody is produced. There is no indication of the particular structural or physical properties of the claimed antibodies, or of any structure/function correlation. And apart from a method step to select for antibodies displaying the particular desired functional characteristics, there is no indication of any specific structural properties required for making the claimed genetically-engineered antibody. There is not even identification of any particular portion of the antibody that must be conserved.

The first paragraph of 35 U.S.C. § 112 "requires a 'written description of the invention' which is separate and distinct from the enablement requirement." *Vas-Cath Inc. v. Mahurkar,* 935 F.2d 1555, 1563 (Fed. Cir. 1991). An adequate written description of a chemical invention "requires a precise definition, such as by structure, formula, chemical name, or physical properties." *University of Rochester v. G.D. Searle & Co., Inc.,* 358 F.3d 916, 927 (Fed. Cir. 2004); *Regents of the Univ. of Cal. v. Eli Lilly & Co., Inc.,* 119 F.3d 1559, 1566 (Fed. Cir. 1997); *Fiers v. Revel,* 984 F.2d 1164, 1171 (Fed. Cir. 1993). "A description of what a material does, rather than of what it is, usually does not suffice." *Rochester,* 358 F.3d at 923; *Eli Lilly,* 119 F.3d at 1568. Instead, the "disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described." *Id.* However, not all functional descriptions "necessarily fail as a matter of law to meet the written description requirement; rather,

the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure." *Amgen Inc. v. Hoechst Marion Roussel, Inc.,* 314 F.3d 1313, 1332 (Fed. Cir. 2003).

In addition, possession of a genus "may be achieved by means of a recitation of a representative number of [compounds]... falling within the scope of the genus." *Eli Lilly,* 119 F.3d at 1569. Possession may not be shown by merely describing how to obtain possession of members of the claimed genus. *See Rochester, supra,* 358.
In this case, there is no description in the instant application nor commonly available in the prior art to sufficiently correlate the desired function – that of inhibiting the aggregation of beta-amyloid, maintaining the solubility of soluble beta-amyloid, or recognizing an epitope within residues 1-28 of beta-amyloid - with that of a particular, known structure. The specification discloses only one mouse monoclonal antibody, AMY-33, which was purchased from ZYMED, San Fransciso, CA, USA (see column 12, lines 4-5) ,and discusses how to select for and make anti-aggregation molecules such as a monoclonal antibody, a single chain monoclonal antibody, a genetically-engineered monoclonal antibody fragment, or a peptide which mimics the binding site of an antibody. There is no description in the claims or in the specification of other species of molecules to support the broad genus of genetically-engineered antibodies. The skilled artisan cannot envision the detailed chemical structure of the encompassed genetically-engineered antibodies, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of selection, isolation, and/or production. Adequate written description requires more than

a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel,* 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016. As noted previously, possession may not be shown by merely describing how to obtain possession of members of the claimed genus. *University of Rochester v. G.D. Searle & Co., Inc.,* 358 F.3d 916, 927 (Fed. Cir. 2004); *Regents of the Univ. of Cal. v. Eli Lilly & Co., Inc.,* 119 F.3d 1559, 1566 (Fed. Cir. 1997).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed."* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). The instant specification discloses only one purchased monoclonal antibody, AMY33, inherently capable of meeting the functional inhibitory requirements of the claims and then describes how to make engineered antibody fragments from this selected antibody. No actual genetically-engineered antibodies or engineered antibody fragments of the selected monoclonal antibodies are disclosed.

Therefore, the full breadth of the claims does not meet the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 103

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

22. Claims 177, 210 and 211 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bickel et al. (*Bioconjugate Chem*. 1994, 5(2): 119-125, of record), as evidenced by Solomon (*Expert Opin Biol Ther*. 2002, 2(8): 907-917, of record), and in view of Ladner et al. ,US Patent No. 4,946,778 (issued August 7, 1990).

The claims are drawn to a therapeutic composition comprising a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and a genetically-engineered antibody, wherein the antibody is obtained by genetically-engineering the DNA encoding a monoclonal antibody that inhibits aggregation of beta-amyloid or maintains the solubility of beta-amyloid and is obtainable using a peptide consisting of β-amyloid 1-28 or recognizes an epitope within residues 1-28 of β-amyloid. Dependent

claims recite that the β-amyloid is human β-amyloid and that the genetically-engineered monoclonal antibody is a single chain antibody. However, the recitation of "a therapeutic composition" and "a pharmaceutical formulation" does not confer any patentable weight because it appears in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). See also MPEP § 2111.02, section II. Accordingly, any prior art pertaining to a composition comprising the claimed antibody and a pharmaceutically acceptable carrier would meet the limitations of the claims.

Bickel et al. teach the development and characterization of a monoclonal antibody, AMY33, which was produced by immunizing animals with residues 1-28 of human β-amyloid (see p. 122, 1st paragraph under Discussion). AMY33 is taught to specifically recognize and bind to residues 1-28 of human β-amyloid (see Figure 2 on p. 122). Bickel et al. also disclose use of the AMY33 antibody diluted in Tris-buffered saline (TBS; see p. 121, 1st column), which meets the limitation of a pharmaceutically acceptable carrier (see, in particular, paragraph 17 the Office action mailed 09/17/2004). In summarizing the background of their publication, Bickel et al. teach that there currently is no noninvasive *in vivo* diagnostic test for the presence of amyloid deposits within the central nervous system. They further suggest that highly specific

anti-β-amyloid monoclonal antibodies could be used for such *in vivo* diagnostic methods, and that these diagnostic tests would be expected to be more specific and sensitive for Alzheimer's disease (AD) than clinical criteria (see p. 119). Bickel et al. also teach that the monoclonal antibody (mAb) AMY33 can be used as a tool to detect cerebral β-amyloid deposits *in vivo* in the brains of patients with AD (see Abstract), and evidence the ability of AMY33 to bind to amyloid deposits in brain sections taken from AD patients (see p. 122, 1st column and Figure 3 on p. 123). Finally, Bickel discusses a need for reducing the immunogenicity of such antibodies and binding proteins targeted to β-amyloid and senile plaques within the brain, as such would facilitate the use of these molecules as neurodiagnostic or therapeutic agents in humans.

While the claimed antibody recites functional properties including inhibition of aggregation of β-amyloid and/or maintaining the solubility of soluble β-amyloid, it is noted that the AMY33 monoclonal antibody taught by Bickel et al. is the same as that described in the instant specification, and is described by the instant specification as possessing such functional characteristics. Additionally, the Examiner notes that antibodies raised against the first 28 amino acids of β-amyloid intrinsically have "chaperone" or anti-aggregating properties, including solubilization of existing β-amyloid aggregates and inhibition of β-amyloid aggregation, as evidenced by Solomon (see p. 909).

Thus while Bickel et al. teach a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a monoclonal antibody obtainable using β-amyloid 1-28 as a peptide immunogen, wherein the antibody is evidenced as being

capable of inhibiting the aggregation of β-amyloid or maintaining the solubility of soluble β-amyloid by Solomon, Bickel does not teach a genetically-modified antibody that is obtained by genetically engineering the DNA encoding the monoclonal antibody, or that the genetically-engineered antibody is a single-chain antibody.

Ladner et al. teaches the production of single chain antibodies and further discloses that they may be used for essentially any use that the prior art has envisioned for monoclonal or polyclonal antibodies (column 3, lines 29-31). Ladner discloses, for example, that single chain antibodies may be used in diagnostics, therapy, *in vivo* and *in vitro* imaging, purification and biosensor applications (column 3, lines 18-24). Ladner teaches the advantages of the use of single chain antibodies to include smaller size, greater stability, reduced cost, and greater ease of genetic modifications to improve binding affinity and specificity (column 3, lines 33-48). Ladner notes that because of the smaller size, single chain antibodies may reduce immunogenicity and thus increase the safety and efficacy of therapeutic applications (column 3, lines 35-38). Further, Ladner teaches that improved affinity will increase the sensitivity of diagnosis and detection, while improved specificity will reduce the number of false positives observed (column 3, lines 45-48). Because a single-chain antibody is a genetically-engineered antibody that is obtained by genetically engineering the DNA encoding a monoclonal antibody, as indicated in the instant claims, the limitations regarding genetically-engineered have been met.

Upon reading the teachings of Bickel et al., the skilled artisan would have recognized the desirability of developing improved compositions comprising the AMY33

antibody for the *in vivo* diagnosis or therapy of Alzheimer's disease. Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to genetically-engineer the monoclonal antibody taught by Bickel et al. to make a single-chain antibody, as taught by Ladner et al., with a reasonable expectation of success in producing a molecule with reduced immunogenicity, improved affinity and sensitivity, greater stability, and reduced cost of production compared to whole antibodies with a reasonable expectation of success. The motivation to do so was expressly provided by Bickel et al., who state at p. 124 that genetically engineering the antibody, such as by humanization, may facilitate the use of the antibodies as neurodiagnostic or therapeutic agents in humans. This was echoed by Ladner et al., who expressly teach that genetically engineered antibodies, such as single chain antibodies, are particularly useful for human therapy. As for the functional properties of the claimed antibodies (i.e., inhibition of β-amyloid and/or maintenance of β-amyloid solubility), it is noted that the instant specification discloses no more than the combined teachings of the above references. Accordingly, the teachings of the above references render obvious the claimed invention of claims 177, 210 and 211.

23. Claims 212 and 213 are rejected under 35 U.S.C. 103(a) as being unpatentable over Majocha et al. US Patent No. 5,231,000 (issued July 27, 1993, of record), as evidenced by Solomon (*Expert Opin Biol Ther*. 2002, 2(8): 907-917, of record), and in view of Boerner et al. WO 91/17769 (published November 28, 1991).

The claims are drawn to a therapeutic composition comprising a pharmaceutically acceptable carrier and a human monoclonal antibody or fragment thereof that inhibits aggregation of β-amyloid or maintains the solubility of soluble β-amyloid, and is obtainable using a peptide consisting of residues 1-28 of β-amyloid as an immunogen, wherein the β-amyloid is human β-amyloid. However, the recitation of "a therapeutic composition" and "a pharmaceutical formulation" does not confer any patentable weight because it appears in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). See also MPEP § 2111.02, section II. Accordingly, any prior art pertaining to a composition comprising the claimed antibody and a pharmaceutically acceptable carrier would meet the limitations of the claims.

Majocha et al. teach the use of the residues 1-28 of human β-amyloid (Aβ 1-28) as an immunogen to generate antibodies, and in particular monoclonal antibodies, to aid in the diagnosis of Alzheimer's disease (column 2, lines 6-16). Majocha notes that monoclonal antibodies can be produced in various ways using techniques well understood by those having ordinary skill in the art (column 3, lines 4-6). The antibodies disclosed by Majocha can be used, for example, for *in vivo* imaging with diagnostically effective labeled antibodies (column 5, lines 3-4). Pharmaceutical

compositions comprising the imaging antibodies for parenteral administration, including the use of pharmaceutical carriers, are also disclosed in the paragraph spanning columns 5 to 6. Majocha demonstrates that monoclonal antibodies prepared using Aβ 1-28 as an immunogen were particularly useful for detecting amyloid deposits in AD brain sections (noted throughout columns 9-11). The Examiner notes that antibodies raised against the first 28 amino acids of β-amyloid intrinsically have "chaperone" or anti-aggregating properties, including solubilization of existing β-amyloid aggregates and inhibition of β-amyloid aggregation, as evidenced by Solomon (see p. 909). Thus, although Majocha et al. is silent with respect to the functional properties of monoclonal antibodies obtained using Aβ 1-28 as an immunogen, such inhibitory properties would necessarily be present in these antibodies as evidenced by Solomon. Moreover, it is noted that Majocha teaches no less than is required by the instant claims.

Thus, Majocha et al. teach a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a monoclonal antibody obtainable using a peptide consisting of residues 1-28 of Aβ as an immunogen. Majocha et al. does not teach that the antibodies are human monoclonal antibodies.

Boerner et al. teach methods for producing antigen-specific, high-affinity human monoclonal antibodies (see title). Boerner notes that in human clinical applications, the use of non-human monoclonal antibodies is not optimal in that rodent antibodies are foreign to the human host, and therefore could be expected to induce host immunity responses. Consequently, Boerner comments, research efforts have endeavored to produce human monoclonal antibodies (p. 3, lines 11-18). As such, Boerner discloses

preparation and culture methods useful for the production of antigen-specific human monoclonal antibodies (see p. 7). Boerner also teaches that such antibodies could serve as diagnostic tools to identify the presence of an antigen specific to a disease state (p. 8, lines 12-16).

Having taken the combined teachings of Majocha et al. and Boerner et al. into account, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to make a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a human monoclonal antibody using Aβ 1-28 as an immunogen with predictable results. Such a pharmaceutical composition would be valuable for diagnosis of Alzheimer's disease. As for the functional properties of the claimed antibodies (i.e., inhibition of β-amyloid and/or maintenance of β-amyloid solubility), it is noted that the instant specification discloses no more than the combined teachings of the above references. Accordingly, the teachings of the above references render obvious the claimed invention of claims 212 and 213.

24. Claims 177 and 210-214 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker et al. EP 0613007 A2 (published 02/22/1993), in view of Cordell (*Annu. Rev. Pharmacol. Toxicol.* Jan 1994, 34: 69-89, reference DL on 11/13/2002 IDS), and Spillantini et al. (*Proc. Natl. Acad. Sci. USA*, May 1990, 87: 3947-3951), as evidenced by Kirschner et al. (*Proc. Natl. Acad. Sci. USA*, Oct 1987, 84: 6953-6957).

The claims are drawn to therapeutic compositions comprising a pharmaceutically acceptable carrier and a human monoclonal antibody (claims 212-213) or a genetically-engineered antibody, such as a single chain antibody (claims 177 and 210-211), wherein the antibody has particular properties and/or production requirements as noted above, and a method for making such a therapeutic composition comprising selection of an appropriate monoclonal antibody, genetic engineering of the DNA encoding said selected monoclonal antibody, and formulation of said genetically engineered antibody into a pharmaceutical formulation (claim 214).

Becker et al. teach a series of assays for evaluating the efficacy of agents which inhibit the neurotoxic effects of β-amyloid peptide, using β-amyloid peptides that have adopted a secondary structure predominantly of the β-sheet conformation (column 1, lines 52-56). Becker teaches that β-amyloid protein, which is the main aggregated molecule found in the amyloid plaques of the brains of Alzheimer's disease patients, is toxic to neurons both *in vitro* and *in vivo* (column 1, lines 1-17 and 30-36). In particular, Becker indicates that results of cell-based neurotoxicity experiments demonstrate a direct correlation between the degree of β-sheet structure in the β-amyloid peptide and its neurotoxicity (column 5, lines 27-30). Thus, Becker notes, the neurotoxicity assays can be supplemented by the incubation of β-amyloid peptides which have adopted a predominantly β-sheet conformation with potential inhibitors of neurotoxicity, such that a reduction in neurotoxicity indicates a candidate inhibitor agent (column 5, lines 34-41). As an example of such an inhibitory agent, Becker discloses conformationally-specific antibodies and antibody fragments which bind to β-amyloid peptides in a secondary

structure-specific manner, such as antibodies that demonstrate specificity for β-amyloid peptides that are predominantly β-sheet in conformation, for use in diagnostics, therapeutics, or in diagnostic/therapeutic combinations (column 5, lines 42-50 and column 7, lines 26-32). Preferred antibodies are those that are useful for the diagnosis and/or treatment of Alzheimer's disease in humans (column 7, lines 49-52). Pharmaceutical formulations containing antibodies having specificity for β-amyloid are disclosed at column 8, lines 19-24, thus meeting limitations regarding pharmaceutical formulations comprising a pharmaceutical carrier. Becker further teaches that the disclosed antibodies may be chimeric, humanized, monoclonal (including human monoclonal), single chain, or genetically-engineered monoclonal antibodies (see columns 5-7). In particular, for administration in humans, genetically engineered antibodies which retain the epitope specificity of monoclonal antibodies are noted to be preferred due to their reduced immunogenicity (column 6, lines 31-40).

The teachings of Becker et al. are echoed by Cordell, particularly with respect to the inhibition of specific β-amyloid peptide species as a therapy for Alzheimer's disease. For example, Cordell notes that adoption of a β-sheet structure by β-amyloid protein is a requirement for aggregation and insolubility (see p. 81, first paragraph). Cordell further states that because small changes in β-amyloid concentration are calculated to have large consequences in the rate of insoluble aggregate formation, therapies that only minimally reduce β-amyloid levels could potentially cause a significant reduction in the number of insoluble deposits (i.e., aggregated β-amyloid) and/or their development into mature plaques. Therefore, Cordell adds, compounds that bind β-amyloid and block its

ability to seed further molecular addition would be of therapeutic advantage (p. 81, first paragraph). Figure 4 on page 82 exemplifies this therapeutic approach, wherein compounds that bind to and inhibit β-amyloid protein aggregation are indicated as therapeutic targets.

Taken together, the teachings of Becker et al. and Cordell corroborate the need for the production of therapeutic formulations, particularly those comprising genetically-engineered antibodies, which specifically bind to and inhibit the aggregation of β-amyloid peptide for the treatment of Alzheimer's disease. However, neither Becker nor Cordell explicitly teach the use of an antibody which is obtainable using a peptide consisting of residues 1-28 of β-amyloid as an immunogen or one which recognizes an epitope within residues 1-28 of β-amyloid.

With the aid of several anti-β-amyloid antibodies capable of recognizing different portions of the human β-amyloid sequence, Spillantini et al. disclose the different configurational states of β-amyloid and their distributions relative to plaques and tangles in Alzheimer's disease (see Abstract and Materials & Methods section). For example, Spillantini demonstrates that the antibody BR88 (raised against residues 1-12 of β-amyloid) labels a large number of tangle-bearing cells, but only a small number of diffuse amyloid deposits, whereas monoclonal antibody 4G8 (raised against residues 17-24 of β-amyloid), stained a large number of diffuse amyloid deposits and plaques in tissue sections from Alzheimer's disease brains (Figure 1 and p. 3949). Spillantini therefore suggests that the epitopes for BR88 and 4G8 are hidden in plaque cores, which probably represent the highest degree of amyloid condensation, whereas it is

accessible in diffuse amyloid deposits and amyloid plaques (p. 3950). This concept is best described in Figure 3 on page 3951, wherein the stages leading to the deposition of β-amyloid in the brains of Alzheimer's disease patients is illustrated. Figure 3 shows that antibodies that recognize epitopes within β-amyloid 1-28 are capable of staining β-amyloid proteins that are in a more soluble state and have not yet formed dense core aggregates. Spillantini further notes that the amino acids 14-28 of β-amyloid are sufficient for amyloid fibril formation *in vitro* (p. 3950, first column), wherein fibrillation precedes aggregation and deposition of β-amyloid. As evidenced by Kirschner et al., the N-terminal region of β-amyloid (i.e., residues 1-28), and in particular the region comprising residues 18-28, is crucial for β-sheet fibril formation and subsequent aggregation of β-amyloid peptide. In summary, the teachings of Spillantini et al. and Kirschner et al. make clear to the artisan of ordinary skill in the art that (1) epitopes on the N-terminal region of β-amyloid are available to antibodies only when the β-amyloid peptide has not yet densely aggregated into solid core deposits and (2) the region comprising residues 14-28 of β-amyloid is necessary for the aggregation of β-amyloid.

In conjunction with the teachings of Becker et al. and Cordell, one of ordinary skill in the art would thus have recognized the therapeutic importance of β-amyloid 1-28, and in particular residues 14-28, as a potential target region for agents to reduce and/or block the formation of β-amyloid peptide fibrils before they aggregate and form dense core deposits. Because residues 14-28 reside within amino acids 1-28 of β-amyloid, an antibody that recognizes an epitope within this region of β-amyloid would meet the

limitation of the instantly claimed antibody. Similarly, it is reasonable to conclude that an antibody raised against β-amyloid 14-28 would be encompassed by and thus meet the limitation of an antibody obtainable using a peptide consisting of residues 1-28 of β-amyloid as an immunogen. The skilled artisan would have been motivated by the prior art teachings to produce a genetically-engineered monoclonal antibody which recognizes an epitope within residues 1-28 of β-amyloid and more specifically within residues 14-28 of β-amyloid (which are notably involved in β-sheet fibril formation), and select for such antibodies that are capable of inhibiting β-sheet formation and reduction of neurotoxicity. β-amyloid peptide that adopts a β-sheet structure forms fibrils which in turn form dense aggregates that are toxic to neurons. Therefore, antibodies directed to the N-terminus of β-amyloid that bind to the β-sheet structure of β-amyloid, inhibit fibril formation, and reduce neurotoxic effects would in effect inhibit the aggregation of β-amyloid and/or enhance the solubility of soluble β-amyloid. One of ordinary skill in the art would therefore have recognized the value of inhibitory antibodies directed to β-amyloid 1-28, and in particular residues 14-28 of β-amyloid, as therapeutic agents for diseases associated with abnormal β-amyloid aggregation and deposition, such as Alzheimer's disease. The methods taught by Becker et al. would have enabled the ordinarily skilled artisan to select for such inhibitory monoclonal antibodies, genetically-engineer them such that they have reduced immunogenicity (or else to produce human monoclonal antibodies from the outset), and subsequently formulate the antibodies into pharmaceutical compositions for the treatment of Alzheimer's disease.

As noted by the United States Supreme Court, if a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. *KSR,* 127 S. Ct. at 1740. "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product is not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show it was obvious under 35 U.S.C. 103." *KSR Int'l Co. v. Teleflex Inc.,* 127 S.Ct. 1727, 1742, 82USPQ2d 1385, 1396 (2007). Accordingly, the combined teachings of the above references would have rendered obvious the instantly claimed invention of claims 177 and 210-214 to a person of ordinary skill in the art at the time of the ivnention.

Conclusion

25. No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Ballard whose telephone number is 571-272-2150. The examiner can normally be reached on Monday-Friday 9 AM - 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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